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Calcification in Colorectal Hepatic Metastases Correlates With Longer Survival

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Background: Calcification occurs in 12–27% of hepatic colorectal metastases, but its clinical significance and its influence on prognosis are unknown.
Methods: All patients diagnosed with colorectal liver metastases at the Ottawa Regional Cancer Centre in 1991 (n = 97), as well as those enrolled in chemotherapy trials in 1990–1992 (n = 51), were entered into a retrospective cohort study. Thirty-six patients were excluded due to inadequate follow-up. In the remaining 112, abdominal CT scans and/or ultrasound examinations were used to determine the presence of calcification. Charts were reviewed for variables, including primary tumour pathology, amount of liver involvement by tumour (<25%, 25–50%, >50%), and the chemotherapeutic agents received, and were subjected to multivariate and regression analysis. End point was survival in months or to December 1993 (median follow up 24 months).
Results: Patients with calcification (n = 31) (28%) were compared to those who did not have calcifications (n = 81). The groups were comparable with respect to sex, age, time to calcification, time to metastases, and treatment type. Calcification occurred independent of the degree of tumour differentiation, the presence of mucinous adenocarcinoma, or the hepatic tumour burden. Nine patients with calcified metastases (30%) had calcification at presentation. Biopsies showed calcification next to viable tumour cells with an absence of an inflammatory reaction. Survival was improved with better primary tumour differentiation and less tumour burden. The presence of calcification had a statistically highly significant improvement in survival ($P < 10^{-6}$, relative risk = .19) independent of other variables.
Conclusions: The presence of calcification within a colorectal liver metastasis appears to imply a significantly better prognosis.
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KEY WORDS: **calcification, survival, colorectal cancer, liver**

INTRODUCTION

Colorectal carcinoma is one of the most common causes of cancer-related deaths in the Western world. In 1992, there were an estimated 16,200 new cases and 6,300 deaths from colorectal cancer in Canada, accounting for >14% of cancer cases in both sexes [1]. The most common site of metastatic spread is the liver, and 10–25% of patients with colorectal carcinoma have liver metastases at time of presentation. Liver metastases develop in 40–70% of patients who die of their disease. Survival with liver metastases is 6–15 months. Length of survival is known to correlate with the degree of differentiation of the tumour primary as well as the volume of tumour present within the liver [2–4].

Calcification is known to occur in 12–27% of liver metastases and is easily identified on both CT scan and ultrasound [5–8] (Fig. 1). The significance of calcification

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Fig. 1. CT scan of a colorectal liver metastasis showing calcification.

in hepatic colorectal metastases is not known, although calcification is thought to be associated with the mucinous variant of colorectal cancer [2]. Isolated case reports of calcification occurring after some forms of chemotherapy also has been reported [9–11]. We observed unusually long survivals in several patients with calcified liver metastases. This study was therefore undertaken to determine if the presence of calcification in hepatic colorectal metastases correlates with survival.

MATERIALS AND METHODS

All patients diagnosed with colorectal liver metastases at the Ottawa Regional Cancer Centre in 1991 (n = 97) and all patients enrolled in chemotherapy trials in 1990–1992 (n = 51) were entered into a retrospective cohort study (n = 148). Thirty-six patients were lost to follow-up, leaving a total of 112 patients. All patients were followed every 3 months to death or to December 1993 (median 24-month follow-up). Diagnostic scans (CT or abdominal ultrasound) were done at that time or sooner if clinically indicated.

Patients were divided into two groups based on the status of their liver metastases at the time of presentation, either with synchronous liver metastases or with metastases metachronous to their colorectal primary. Patients were further subdivided based on whether or not they had calcification of their hepatic metastases. Patients were considered to have calcification if they presented with calcified liver metastases or if they developed it in follow-up. Thus four groups were considered: Group 1: patients with liver metastases when diagnosed with their colorectal primary in whom the metastases calcified, Group 2: those patients who presented with liver metastases that did not calcify, Group 3: patients without liver metastases at diagnosis of their colorectal primary, who later developed metastases with calcification, Group 4: patients without liver metastases at presentation of their colorectal primary who developed metastases which did not calcify.

Patient charts were reviewed and variables were obtained, including time to metastases, time to calcification if present, type of chemotherapy received, and pathology of the primary tumour. The pathology of the tumour was defined as to type and degree of differentiation, i.e., well differentiated, moderately differentiated, poorly differentiated, mucinous adenocarcinoma. Ultrasound and/or CT scans of all patients were seen by a radiologist who was unaware of the type of treatment or outcome, and the presence of calcification was determined. The amount of hepatic tumour involvement at the time of the diagnosis was estimated as <25%, 25–50%, and >50% of the liver,

TABLE I. Patient Characteristics: Calcification in Colorectal Hepatic Metastasis Study

Variable	Group 1	Group 2	Group 3	Group 4
Number (n = 112)	15	32	16	49
Male/female	12/3	24/8	12/4	32/17
Age (mean ± SD)	60 ± 13	65 ± 12	64 ± 9	63 ± 10
Time to metastasis in mo. (mean ± SD) after diagnosis of colorectal primary			26.9 ± 18	21.8 ± 19
Time to calcification in mo. (mean ± SD) after metastasis found	5.7 ± 8		6.5 ± 10	
Pathology of colorectal primary (adenocarcinoma)				
well differentiated	5	6	4	5
moderately differentiated	8	22	8	15
poorly differentiated	2	8	1	4
mucinous	0	7	2	6
not available	1	6	0	2
Amount liver involvement				
<25%	6	10	5	15
25–50%	6	18	7	9
>50%	2	15	1	7
not available	2	6	2	1
Treatment type				
5-FU/FA[a]	4	8	5	4
PALA/5-FU/FA[b]	2	3	1	4
other	1	8	3	9
none	9	3	6	15

[a]5 FU = 5 fluorouracil, FA = folinic acid
[b]PALA = N-phosphonoacetyl L-aspartic acid.

TABLE II. Calcification in Liver Metastasis Survival Analysis of Variables

Variable	Relative risk	95% Confidence limits		*P* value
Calcification	.19	.13	.40	$<10^{-6}$
Extent of liver involvement with metastasis	2.05	1.08	3.08	.02
Pathology	.36	.18	.80	.01
Age	1.0	.97	1.02	.82
Sex	1.41	.86	2.15	.14
Metastasis at diagnosis	.93	.82	1.52	.75

since this method has been shown to estimate reliably the tumour burden of the liver and to allow comparison among the groups [4]. The endpoint was survival in months or to December 1993. Logistic regression analysis was used to determine the association of calcification with other variables. Proportional hazard analysis (Cox regression) was used to examine the effect of calcification and other variables on the length of survival.

RESULTS

The groups were comparable with respect to sex, age, time to calcification, and, in groups 3 and 4, time to metastases. Treatment type, primary tumour pathology, and amount of liver involvement were also comparable. The majority of patients received some form of chemotherapy (Table I).

Thirty-one patients (28%) of 112 had calcification in their colorectal hepatic metastases. Using a logistic regression analysis, calcification was unrelated to the pathology of the colonic primary, including mucinous adenocarcinoma. The extent of liver involvement did not correlate with the development of calcification, i.e., small liver secondaries did not calcify more readily than large ones. Receiving chemotherapy did not correlate with the development of calcification.

By multivariate analysis, survival correlated with the pathological grade of the primary colorectal tumour, i.e., the more differentiated the tumour, the longer the survival ($P = .01$). The greater the amount of liver involved by tumour, the worse the survival ($P = .02$). Although not the object of this study, a comparison of different chemotherapy regimens did not correlate with survival.

The presence of calcification, however, was associated with a substantial and highly statistically significant improvement in survival ($P < 10^{-6}$, relative risk = .19), independent of other variables (Table II, Fig. 2).

DISCUSSION

Survival of patients with colorectal metastases is known to correlate with the degree of differentiation of the colonic primary and with the amount of liver involvement by tumour [2]. This has been borne out in our retrospective study.

Mucinous adenocarcinoma is reported to have a worse prognosis and is believed to correlate with the develop-

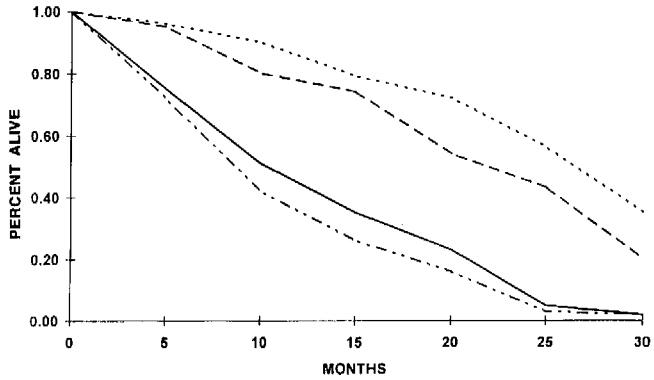

Fig. 2. Survival from diagnosis of metastasis. This graph correlates the percentage of patients alive at a given time to the survival in months. At 30 months, 30–40% of patients with calcifications are alive, as compared to none in the groups with no calcification.

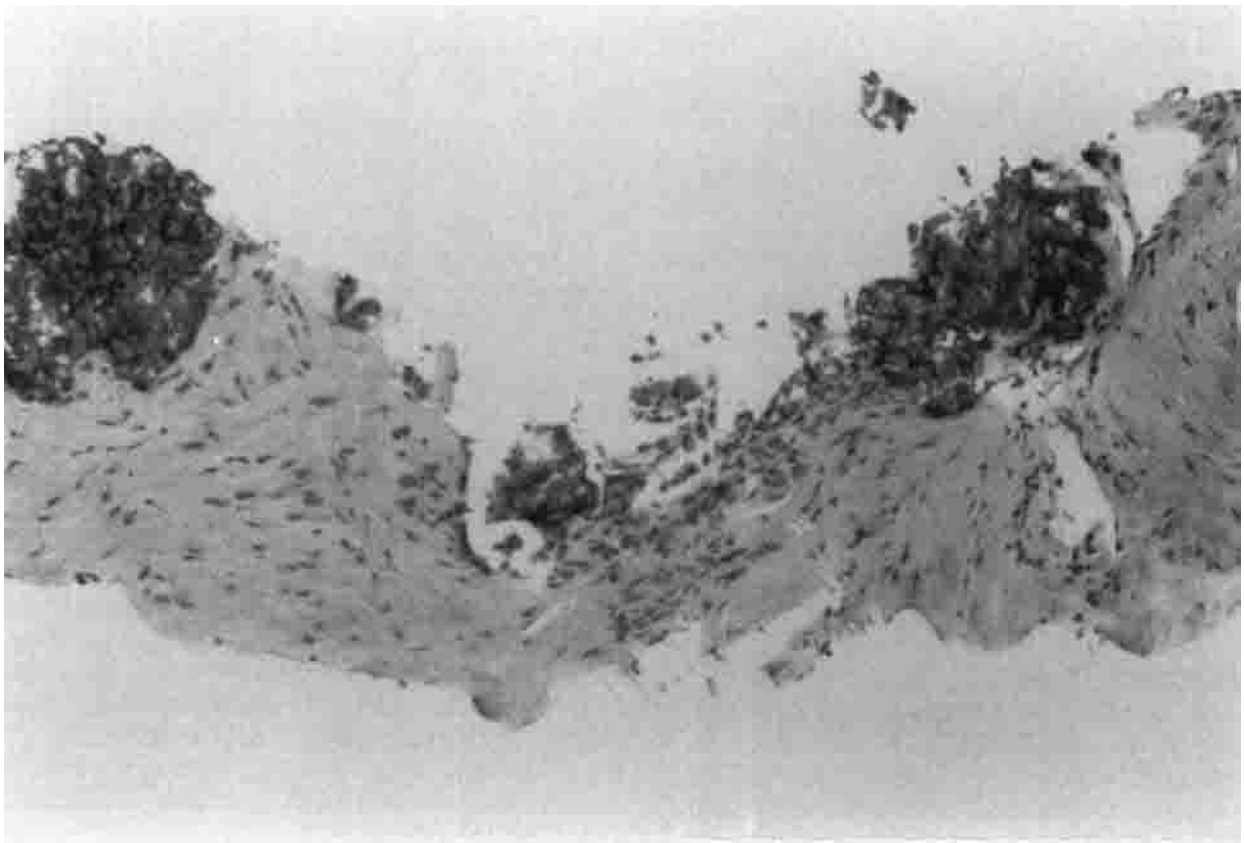

Fig. 3. Biopsy of a calcified liver metastasis.

ment of calcification. We found no correlation between the presence of mucinous adenocarcinoma, the development of calcification, or survival. The incidence of mucinous adenocarcinoma was 13% in our study, well above the reported 5% incidence [2].

Many of the patients included in the study were patients involved in a randomised clinical trial by the Ottawa Regional Career Centre comparing the use of a PALA, 5-FU, FA regimen vs. 5-FU, FA for the treatment of metastatic colorectal cancer. This regimen has subse-

quently been shown not to improve survival over the standard 5-FU, FA regimen, and its use has been abandoned.

We could not correlate the type or response to chemotherapy with the occurrence of calcification. Almost half (7 of 16 patients) of patients with calcified liver metastases had calcification spontaneously prior to any therapy. The nine patients who developed it after therapy was begun received a wide variety of treatments and did not differ in this respect from patients who did not develop calcification. The majority of the patients did not develop them at all. The pathophysiology of this is unclear. It may represent the body's attempt to destroy the tumour with subsequent tissue necrosis, resorption, and ultimately calcification. This is believed to be the reason for calcification in various benign conditions. To look at this hypothesis, biopsies of the calcified metastases were obtained in two patients (Fig. 3). These showed calcification directly next to viable tumour cells with an absence of an inflammatory reaction, inconsistent with this hypothesis. Interestingly, calcification is not known to occur within the colorectal primary itself, or within colorectal metastases in other sites (lung, bone, brain). It appears to be a characteristic of the individual tumour. Understanding the pathophysiology of this phenomenon may have a profound impact on the ability to treat these tumours and opens the door to further investigation.

The novel finding of this study is that the presence of calcification within a colorectal liver metastases implies a significantly longer survival independent of other variables. This has not previously been reported. Increased survival with calcified colorectal liver metastases has important implications for the prognosis and management of these patients, e.g., in the selection of patients for surgical resection and/or adjuvant chemotherapy protocols. This may improve the dismal median 6 months survival and the 30% 5-year survival rate for resectable colorectal liver metastases for selected patients.

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